

REMARKS

Claims Under Examination

Claims 56 – 88 are under consideration in the Office action mailed December 6, 2005. Claims 89 – 134 are withdrawn from consideration at this time. Applicant reserves the right to prosecute the withdrawn claims in a related application, such as a divisional or continuation application.

Priority

On page 3 of the Office action, the Examiner acknowledges Applicant's claim for foreign priority based on applications 99 0033 and 99 0782, filed on January 15, 1999 and September 20, 1999, respectively. The Examiner indicates that Applicant has not filed certified copies of the two applications, as required by 35 U.S.C. 119 (b). In U.S.S.N. 09/903,681, which is the parent of the subject application, Applicant filed a "Substitute" Declaration and Power of Attorney, which includes a claim to priority to the two referenced applications filed in Ireland. In the Office Action Summary mailed August 25, 2003 (Paper No. 9) in U.S.S.N. 09/903,681, the Examiner acknowledged a claim for foreign priority under 35 U.S.C. 119(a)-(d) or (f) (item 13) a) indicates that "Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a))." In order to be sure that the record is complete and the correct documents in the file, Applicant is submitting with this Amendment a certified copy of each of the referenced applications to which priority is claimed. Receipt of those documents is requested.

Information Disclosure Statement

At page 3 of the Office action, the Examiner indicates that the Information Disclosure Statement filed 7/27/2004 fails to comply with 37 CFR 1.98(a)(2) for the reasons stated and that both Information Disclosure Statements filed 2/23/2004 fail to comply with 37 CFR 1.98(a)(1) for the reasons stated. The Information Disclosure Statements have been placed in the application file, but the information referred to has not been considered.

The Information Disclosure Statements are very lengthy and it is unfortunate that the references were not considered. An Information Disclosure Statement, which cites all of the

documents cited in the three previously-filed Information Disclosure Statements and additional documents and is accompanied by a copy of each of the documents cited, is being filed with this reply. The Examiner indicated, in a telephone conversation with Applicant's attorney, that she would prefer to have an Information Disclosure Statement and the cited references filed.

Specification

The Preliminary Amendment mailed 12/30/04 contained typing errors, in that it incorrectly referred to the deposited *Bifidobacterium longum infantis* strain as HCC 35624 and the deposited *Lactobacillus salivarius* strain as HCC 118. These should be, respectively, UCC 35624 and UCC 118. The errors have been corrected by this Amendment.

Claim Objections

Claims 56-88 are objected to because of informalities. Specifically, claims 56 and 60 were objected to because the Latin name was not in italics. These informalities have been corrected by this Amendment.

Claim Rejections – 35 USC §112

Deposit

Claims 56-88 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner indicates that, due to typing errors, as described at page 5 of the Office action, the deposit issues and requirements are not fully satisfied.

In the Second Preliminary Amendment mailed 12/30/04, at page 12, there is a Statement of Biological Culture Deposit, in which Applicant's then representative stated:

Applicant respectfully submits that (1) a deposit of *Bifidobacterium longum infantis* strain HCC 35624 was made at the National Collections of Industrial and Marine Bacteria Limited (NCIMB) at Ferguson Building, Craibstone Estate, Bucksburn, Aberdeen AB21 9YA, UK on January 13, 1999 and accorded the accession number NCIMB 41003; and (2) a deposit of *Lactobacillus salivarius* strain HCC 118 was made at the National Collections of

Industrial and Marine Bacteria Limited (NCIMB) at Ferguson Building, Craibstone Estate, Bucksburn, Aberdeen AB21 9YA, UK on November 27, 1996 and accorded the accession number NCIMB 40829. Enclosed please find the copies of the receipts and viability reports regarding the above-indicated deposits for Examiner's reference.

The undersigned attorney, on behalf of the Applicant of the present invention, hereby state that (1) the deposit of *Bifidobacterium longum infantis* strain HCC 35624 with the accession number NCIMB 41003 and *Lactobacillus salivarius* strain HCC 118 with the accession number NCIMB 40829 at the National Collections of Industrial and Marine Bacteria Limited (NCIMB) has been made under the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure; and (2) all restrictions imposed by the depositor on all restrictions to the availability to the public of the culture so deposited will be irrevocably removed upon the granting of the patent.

For clarification: The number used by Applicant to identify the *Bifidobacterium longum infantis* strain is UCC 35624. This strain was deposited with NCIMB on January 15, 1999 and given Accession Number 41003. The National Food Biotechnology Centre (NFBC) was a research center which operated within the University College Cork-National University of Ireland, Cork (UCC). The strain was deposited on behalf of UCC by the National Food Biotechnology Centre and the reference number NFBC 35624 (not UCC 35624) was mistakenly used on the deposit form (Form BP/4 (sole page)). NCIMB 41003 is the Accession Number for UCC 35624 (which additionally had been referred to as NFBC 35624).

In the Statement on page 12 of the Preliminary Amendment (reproduced above), Applicant's then representative incorrectly referred to UCC 35624 as HCC 35624 and incorrectly referred to UCC 118 as HCC 118. In the Statement on page 12 of the Preliminary Amendment, wherever "HCC 35624" appears, it should read (be replaced with) UCC 35624 and wherever "HCC 118" appears, it should read (be replaced with) UCC 118. Applicant hopes that this is sufficient clarification. If it is not, upon request from the Examiner, Applicant will submit a revised, correct Statement.

Indefiniteness

Claims 70, 81, and 83 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Specifically, claim 70 is rejected for the recitation of a “‘genetically modified mutant’ of *Lactobacillus* strain UCC 118.....” It is the Examiner’s assessment that it is “unclear what genetic mutation is intended in the lack of specific definitions in the as-filed specification.” Applicants disagree. A genetically modified mutant of the UCC 118 *Lactobacillus* strain and the deposited strain differ in their respective genomic compositions (DNA sequences); they exhibit substantially the same therapeutic effect.

The Examiner states that “Claims 88 and 83 recite the use of some additional ‘bacterial component’ and ‘bacterial compound’ respectively. To clarify, claim 81 recites the term “bacterial component” and Claim 83 recites the term “biological compound.” The Examiner states that it is “unclear what bacterial cells and/or extracts” are intended to be used in combination with the claimed bacterial strain.

Claim 81 recites the term “bacterial component.” A bacterial component is obtained or derived from a bacterium, such as one of the deposited strains. A bacterial component can be obtained from the bacterium using known methods, such as that described in Example 9, and assessed for its activity (e.g., its effect on immune parameters, cytokine levels, inflammation) using known methods, such as those described in the subject application. A bacterial component derived from the bacterium is one which is produced using a component of the bacterium, such as bacterial DNA or information about or obtained from the bacterium, such as the sequence of bacterial DNA or protein. For example, bacterial DNA encoding a factor shown to have desirable activity can be used in known methods to produce the encoded factor or the DNA or protein sequence can be used to synthesize the component. The bacterial component can be incorporated into a formulation which also comprises *Bifidobacterium* NCIMB 41003, resulting in the formulation of claim 81.

Claim 83 recites the term “biological compound.” A biological compound is any compound (e.g., a carbohydrate, a lipid, a protein, nucleic acid) which is either obtained from a biological source, such as a cell or tissue, using known methods, or derived from a biological

source, as described above with reference to the term “bacterial component.” For example, a biological compound derived from a cell or tissue is one which is produced using a component of the cell or tissue, such as DNA or information about or obtained from the cell or tissue, such as the sequence of DNA or protein or the composition and structure of a carbohydrate present in the cell. A biological compound can be used in combination with the claimed strain in order, for example, to induce or enhance the activity of the microorganism. The biological component can be incorporated into a formulation which also comprises *Bifidobacterium* NCIMB 41003, resulting in the formulation of claim 83.

Claim Rejections under 35 USC §102(b) or §103(a)

Cavaliere et al., U.S. 6,077,504

Claims 56 - 62 and 72 - 88 are rejected under 35 U.S.C. §102(b) as anticipated by or, in the alternative, under 35 U.S.C. §103(a) as obvious over U.S. Patent No. 6,077,504 (Cavaliere et al.), for the reasons set forth at pages 6 – 8 of the Office action.

The Examiner’s description of U.S. 6,077,504 is set forth at pages 6 – 7 of the action. The Examiner states that the cited patent is “considered to anticipate the claims (sic) invention because it teaches identical bacterial strain(s) and compositions with these strains wherein the strains belong to the genus of *Bifidobacterium* including strains *Bifidobacterium longum* ATCC 15707 and *Bifidobacterium infantis* ATCC 15697 which are characterized by identical essential features and/or effects including immunomodulation and protection from pathogens as the claimed strain/composition. Consequently, the claimed strain/formulation with the strain UCC 35624 belonging to *Bifidobacterium sp.* appears to be anticipated by the cited documents.”

The Examiner continues by stating that “even if the claimed strain UCC 35624 is not identical to the referenced strains with regard to some unidentified characteristics, the differences between that which is disclosed and that which is claimed are considered to be so slight that the referenced microorganisms are likely inherently possess (sic) the same characteristics of the claimed strain UCC 35624 particularly in view of the similar characteristics which they have been shown to share such as assignment to the same genus and capability of producing immunomodulatory and antimicrobial effects. Thus, the claimed strain UCC 36624 (sic) and

formulations with this strain would have been obvious to those of ordinary skill in the art within the meaning of USC 103.” (Office action, pp. 7 – 8).

In support of these rejections, the Examiner relies on the “assignment to the same genus” of the strains of Cavaliere et al. and NCIMB 41003 (strain UCC 35624). It is well known that there are many species which are included within the genus—30 or more characterized species, in fact—and that within each species, there are many strains. For example, a quick search of the ATCC website shows that there are 10 deposits of strains within the *Bifidobacterium longum* species alone. Reuter explains that “Each person will have an individually fixed microflora as far as qualitative structure and the quantities of lactobacilli and bifidobacteria are concerned (Reuter, 1963 1965a, b). This fact is of great interest, as more than 400 species within the intestinal microflora can be identified... (Mitsuoka, 182, 1992; Tannock, 1999a).” Reuter, Gerhard. Current Issues in Intestinal Microbiology 2001. 2(2) 43-44.

Classification of microorganisms, including those of Cavaliere et al. and Applicant, in the same genus (*Bifidobacterium*) is based on the fact that they are anaerobic, gram-positive, irregular or branched rod-shaped bacteria found in the intestine. This genus encompasses many species and innumerable strains. As discussed below, the characteristics of strains within the genus are determined/influenced by the source from which they are obtained.

Cavaliere et al. (U.S. 6,077,504) does not anticipate or render obvious claim 56, which requires the specific *Bifidobacterium* strain deposited at the NCIMB under accession number 41003. Claim 56 and claims dependent thereon are clearly not anticipated by U.S. 6,077,504. The Cavaliere et al. patent describes bacterial strains *Bifidobacterium longum* ATCC 15707 and *Bifidobacterium infantis* ATCC 15697, both of which are of fecal origin. See, for example, Scardovi V. in Bergey’s Manual of Systemic Bacteriology, page 1424: Type strain ATCC 15707 (E 194b from feces of an adult human (Reuter, 1971)) and Type strain ATCC 15697 (S12 from feces of a human infant (Reuter 1971)). A copy of the cited reference is provided for the Examiner’s convenience. As is discussed below, it is well known that the source of a *Bifidobacteria* strain is key in determining its characteristics. The strains of Cavaliere et al. were isolated from sources different from the source of Applicant’s claimed strain. In addition, Applicant is providing, in the form of a Declaration of Liam O’Mahony, Ph.D. (Declaration), results that demonstrate that the strains differ significantly in their immunomodulatory effects

and that their genomes differ as well. Briefly, as discussed in the Declaration, the strains of Cavaliere et al. and Applicant's claimed strain have different effects on cytokine levels; they have different effects on the immune response and, clearly, are not "identical [in] essential features and/or effects including immunomodulation," as the Examiner has concluded. In fact, the strains of Cavaliere et al. exhibit immunomodulatory effects (stimulation of anti- and pro-inflammatory cytokines) which are inappropriate for use in treating the symptoms of irritable bowel syndrome. Also presented in the Declaration are results of assessments that show that Applicant's strain and the strains of Cavaliere et al. differ in both a specific genomic sequence and repetitive genomic sequences, further demonstrating that they are not the same. See Exhibit 3. (Please note that the a faxed version of the Declaration is being filed with this Amendment. The originally signed Declaration is being sent to the undersigned and can be provided to the Examiner, if she would like the undersigned to do so.)

In sharp contrast to the strains of Cavaliere et al., Applicant's claimed strain, NCIMB 41003, was adherent to the healthy gastrointestinal tract of an individual with no associated pathology. It was isolated from washed sections of the gastrointestinal tract obtained during reconstructive surgery, as described in Example 1 of the subject application. Fecal flora (such as that represented by the strains of Cavaliere et al.) represent the luminal contents of the distal large bowel (colon). In contrast, microflora adherent to the mucosa represent a highly specialized microenvironment. For example, strains adherent to the mucosa must be able to survive in a more aerobic environment than occurs in the lumen, which is anaerobic. Strains adherent to the mucosa, such as Applicant's claimed strain, are exposed to oxygen as a result of the fact that they adhere to the mucosa, which are oxygenated by the underlying blood vessels. Further, adherent strains thrive in an immunologically hostile environment, which is not the case for nonadherent strains (those which are present, for example, in the colon or feces, such as those described by Cavaliere et al.).

It is well known that the source of a Bifidobacteria strain is key in determining its characteristics. For example, the population of bifidobacteria in the gastrointestinal tract is known to be influenced by several factors, such as diet, antibiotics and stress. As Reuter explains,

The gastrointestinal microflora is a very complex community. Within the gastrointestinal tract, different habitats have to be recognized, e.g. mouth,

stomach, small intestine (especially lower jejunum and ileum), large intestine (caecum, colon) and rectum. Normally, near stability exists in these habitats. The balance is influenced primarily by the host's individuality....Each person will have an individually fixed microflora as far as qualitative structure and the quantities of lactobacilli and bifidobacteria are concerned (Refs). This fact is of great interest, as more than 400 species within the intestinal microflora can be identified and may attain population levels nearly as high as 10^{12} /g in the colon (Refs). Reuter, Gerhard. Current Issues in Intestinal Microbiology 2001. 2(2) 43.

Reuter continues by stating:

Some reports in the literature ignore the differences of the intestinal microflora between infants on one hand, and adults and elderly people on the other. In these age groups, lactobacilli and bifidobacterial populations are substantially different in structure and quantities. While lactobacilli are changing only quantitatively, probably after they have randomly colonized immediately after birth, the development of the bifidobacteria microflora is influenced by nutritional factors also (e.g. in-breast fed or formula-fed infants) or by the age of an individual. Reuter, Gerhard. Current Issues in Intestinal Microbiology 2001. 2(2) 44.

Further evidence that the source of a Bifidobacteria strain is key in determining its characteristics and, thus, that strains from different sources are different is found, for example, in Eckberg et al., "Diversity of the Human Intestinal Microbial Flora" Science Vol. 308 10 June 2005 (which illustrates the diversity of the human flora and the differences between the mucosa associated flora and stool flora and discussed the finding that nearly all mucosal libraries from two of three healthy adult humans were significantly different from the corresponding stool library). See also Backed et al., "Host-Bacterial Mutualism in the Human Intestine" Science Vol. 307 25 March 2005 (copy provided), which further shows that one cannot infer that bacteria assigned to a genus or species have similar characteristics, since many different strains may be included within even a single species. Further, see Sonnenburg et al. "Glycan Foraging In Vivo by an Intestine-Adapted Bacterial Symbion" Vol. 307 25 March 2005.

As presented briefly above, Applicant is providing information that clearly demonstrates that the strains of Cavaliere et al. are different from Applicant's strain, NCIMB 41003. This information, provided in the form of a Declaration of Liam O'Mahony, Ph.D., makes it clear that the two strains of Cavaliere et al. and Applicant's strain NCIMB 41003 (UCC 35624) differ in "essential features," such as immunomodulation. Specifically, a peripheral blood mononuclear

cell (PBMC) cytokine stimulation assay was performed to compare the strains disclosed in U.S. 6,077,504 and strain NCIMB 41003. Results of the assay demonstrate that the strains differ significantly in their immunomodulatory effects. As shown, stimulation of IL-10 by strain NCIMB 41003 is greater than IL-10 stimulation by either strain (ATCC 15707; ATCC 15697) disclosed by Cavaliere et al.; stimulation of IL-10 by NCIMB 41003 is significantly greater than stimulation of IL-10 by ATCC 15707 (Figure 1 of Exhibit 2 of the Declaration). Stimulation of IL-12 by ATCC 15707 is significantly different from stimulation of IL-12 by NCIMB 41003; the former stimulated IL-12 and the latter did not (Figure 2 of Exhibit 2 of the Declaration). Clearly, ATCC 15707 and NCIMB 41003 are different organisms that differ in their immunomodulatory effects. The extent to which ATCC 15707 stimulates the anti-inflammatory cytokine IL-10 is significantly less than the extent of IL-10 stimulation by NCIMB. In contrast, ATCC 15707 stimulates the proinflammatory cytokine IL-12 and NCIMB 41003 does not.

A further key difference between the two strains described by Cavaliere et al. and NCIMB 41003 is clearly represented graphically in Figure 3 of Exhibit 2 of the Declaration, which shows their respective effects on TNF- α . As shown, both ATCC 15707 and ATCC 15697 stimulate TNF- α in PMBCs; NCIMB 41003 has only a slight impact on TNF- α production. The difference in stimulation of this pro-inflammatory cytokine by ATCC 15707 and ATCC 15697 is significantly greater than stimulation by NCIMB 41003. The two strains of Cavaliere et al. differ significantly from Applicant's strain in this important immunomodulatory effect.

Further evidence of critical differences between the strains disclosed in U.S. 6,077,504 and NCIMB 41003 is presented in Figure 4 of Exhibit 2 of the Declaration. As shown, the ratio of IL-10 to TNF- α (the ratio of anti-inflammatory cytokine IL-10 to pro-inflammatory cytokine TNF- α) is significantly greater for NCIMB 41003 than for either ATCC 15707 or ATCC 15697. In other words, the Cavaliere et al. strains exhibit a significantly lower anti-inflammatory to pro-inflammatory cytokine ratio than that of NCIMB 41003. The Cavaliere et al. strains and Applicant's strain differ in their immunomodulatory effects--key characteristics of the strains. As Dr. O'Mahony explains in the Declaration, selection of a bacterial strain useful for the treatment of irritable bowel syndrome (IBS) required a strain that possessed a high anti-inflammatory to pro-inflammatory cytokine ratio. Strains with low anti-inflammatory to pro-inflammatory cytokine ratios, such as the strains of Cavaliere et al., would not improve the

symptoms (be useful in the treatment of) patients with IBS. The Examiner's attention is respectfully directed to item 5 of the Declaration for further discussion of this aspect of the strains.

Such differences in immunomodulatory effects between the Cavaliere et al. strains and Applicant's strain are important considerations in the use of the strains. In related research, Applicant and co-workers hypothesised that the PBMC cytokine response would be useful for predicting which probiotic strains would have *in vivo* efficacy. On the basis of its ability to induce high levels of IL-10 (anti-inflammatory cytokine), coupled with its low level of TNF- α induction (pro-inflammatory cytokine), *Bifidobacterium infantis* 35624 (NCIMB 41003) was selected for the treatment of IBS patients. Following consumption of this probiotic (*Bifidobacterium infantis* 35624), there was a significant improvement in IBS symptoms in patients, in whom the imbalance in pro-inflammatory:anti-inflammatory cytokine ratio was normalised. In contrast, treatment of IBS patients with *Lactobacillus salivarius* UCC1, which has a different cytokine profile, did not result in such an improvement in symptoms. The imbalance in the corresponding cytokine ratio did not normalise in patients treated with *Lactobacillus salivarius* UCC1 or in patients treated with a placebo. See, O'Mahony et al., *Gastroenterology* 2005; copy provided with this reply. This comparison has been repeated in a large multi-centre placebo controlled clinical trial involving approximately 300 IBS patients and, again, efficacy of *Bifidobacterium infantis* 35624 (NCIMB 41003) was shown. (Whorwell et al., *American Journal of Gastroenterology*, in press). Based on the PBMC cytokine profiles obtained with 15697 and 15707 (see above), these strains would not be expected to be efficacious in the treatment of IBS patients but, instead could worsen IBS symptoms, since both strains induce significant secretion of the pro-inflammatory cytokine TNF- α . In addition, ATCC 15707 does not induce sufficient amounts of the anti-inflammatory cytokine, IL-10, which would have a beneficial effect on IBS symptoms.

For at least the reasons presented above, it is clear that the strains of Cavaliere et al. are different from Applicant's claimed strain in key respects and that neither of the prior art strains anticipates NCIMB 41003. Removal of the rejection, under 35 U.S.C. §102(b), of claim 56 and

of claims 57-62 and 72-88, all of which depend, directly or indirectly, on claim 56, is respectfully requested.

The Examiner asserts that “even if the claimed strain UCC 35624 is not identical to the referenced strains with regard to some unidentified characteristics, the differences between that which is disclosed and that which is claimed are considered to be so slight that the referenced microorganisms are likely inherently possess (sic) the same characteristics of the claimed strain UCC 35624 particularly in view of the similar characteristics which they have been shown to share such as assignment to the same genus and capability of producing immunomodulatory and antimicrobial effects. Thus, the claimed strain UCC 36624 (sic) and formulations with this strain would have been obvious to those of ordinary skill in the art within the meaning of USC 103.” (Office action, pp. 7 – 8)

This is clearly not correct. As discussed above, the claimed strain (UCC 35624) differs from both strains described in U.S. 6,077,504 in several key respects, such as the sources from which they were obtained; their effects on production of cytokines which play important roles in inflammation; and their DNA sequences. The referenced microorganisms (ATCC 15707 and ATCC 15697) do not, as the Examiner contends, possess the same characteristics as NCIMB 41003. In addition, the differences between the strains of Cavaliere et al. and NCIMB 41003 are not, as the Examiner proposes, slight. In fact, as clearly described above, the microorganisms described by Cavaliere et al. and Applicant’s claimed strain differ significantly in their respective immunomodulatory effects. The strains of Cavaliere et al. do not inherently possess “the same characteristics of the claimed strain UCC 35624,” as the Examiner proposes in the Office action. In fact, the Cavaliere et al. strains have immunomodulatory effects (effects on stimulation of key cytokines) opposite to those of Applicant’s claimed strain and teach away from selecting an organism, such as NCIMB 41003, which has a higher anti-inflammatory to pro-inflammatory cytokine ratio than that of the Cavaliere et al. strains. Analysis of the three strains showed that their DNA sequences differ, both in a specific sequence and a repetitive sequence, which is further evidence that the Cavaliere et al. strains and Applicant’s strain are different and that they do not, as the Examiner concludes, possess the same characteristics. Withdrawal of the rejection of claims 56-62 and 72-88 under 35 U.S.C. §103(a) as obvious over U.S. Patent No. 6,077,504 is respectfully requested.

Chen et al., U.S. 6,368,591

Claims 56-62 and 72-88 are rejected under 35 U.S.C. §102(b) as anticipated by or, in the alternative, under 35 U.S.C. §103(a) as obvious over Chen et al. (U.S. Patent No. 6,368,591). The Examiner's description of U.S. 6,368,591 is set forth at pages 8 - 9 of the action. There, the Examiner states, in part, that the cited patent "disclose (sic) the strain belonging to the genus of *Bifidobacterium* including strain *Bifidobacterium longum* strain 6-1 (CCTCC Number M 98004 (sic)) which inhibits growth of Gram positive and/or Gram negative bacteria including *Staphylococcus sp.* and coliforms (col. 6, lines 56-58), which is a gastrointestinal bacteria (col. 4, lines 61-640 (sic), which produces immunomodulatory effects upon oral consumption or regulates immunologic function, decreases abnormal level of cytokine expression (col. 14, lines 43-60), which is effective in treating inflammation including diarrhea (col. 14, line 31)." The Examiner concludes that the cited patent "is considered to anticipate the claimed invention because it teaches identical bacterial strain and composition with this strain wherein the strain belongs to the genus of *Bifidobacterium* and, thus, characterized by identical essential features and/or effects." (Applicant notes that the correct reference number for *Bifidobacterium longum* strain 6-1 is CCTCC Number M 98003, not CCTCC Number M 98004, as indicated in the Office action. See, for example, U.S. 6,368,591, col. 7, lines 11 - 13.)

U.S. 6,368,591 does not anticipate or make obvious Applicant's claimed invention. Claim 56 requires the *Bifidobacterium* strain deposited at the NCIMB under accession number 41003. The Examiner seems to conclude that the cited patent teaches a bacterial strain that is identical to NCIMB 41003 because the bacterial strain of U.S. 6,368,591 and NCIMB 41003 belong to the same genus (*Bifidobacterium*) and are "thus, characterized by identical essential features and/or effects." This is simply not correct. It is well known that there are many species of *Bifidobacterium*, that there are innumerable strains within the *Bifidobacterium longum* species and that, as discussed above, the characteristics of a specific strain are determined by the source from which it is obtained. In fact, Applicant has shown, as discussed above, that *Bifidobacterium* strains differ in their characteristics. (See the discussion and data demonstrating the differences among the three strains (two prior art strains of Cavaliere et al. and Applicant's strain) discussed with reference to Cavaliere et al, above (U.S. 6,077,504)).

Further evidence of the differences between *Bifidobacterium* strains is evident in the Chen et al. 6,368,591 patent cited by the Examiner. Differences in physicochemical characteristics of *Bifidobacterium longum* and *Bifidobacterium longum* strain 6-1 are shown in Table 1 of U.S. 6,368,591. The physicochemical characteristics of the Chen et al. *Bifidobacterium longum* strain 6-1 and Applicant's strain NCIMB 41003 are also noticeably different, which is further evidence that the microorganisms are not the same. As described in the accompanying Declaration, a comparison of the physicochemical characteristics of the Chen et al. *Bifidobacterium longum* strain 6-1 and those of Applicant's strain (NCIMB 41003) show that they differ in at least two significant features of their carbohydrate utilization profiles. The Briefly, the carbohydrate utilization profile of NCIMB 41003 was assessed through cultivation on modified deMann Rogosa Sharpe (MRS) agar plates, in which the chief carbon source (dextrose) was replaced with the sugar whose utilization was being assessed. Conditions under which assessment of the physicochemical characteristics of *Bifidobacterium longum* strain 6-1 was carried out (as described in the Chen et al. patent) were reproduced. (As explained in the Declaration, it has not been possible to obtain the *Bifidobacterium longum* strain 6-1 and, thus, a side by side/direct assessment has not been possible. See item 8 of the Declaration.) This analysis showed that NCIMB 41003 (UCC 35624) was able to grow on all of the sugars assessed except fructose and, in contrast, *Bifidobacterium longum* strain 6-1 showed no growth on either sucrose or mannose. Clearly, the two strains differ in carbohydrate fermentation. These differences mean, for example, that the genomes of the two strains also differ. See item 8 of the Declaration.

Bifidobacterium longum strain 6-1 (CCTCC Number M 98003) was obtained from feces described as selected from healthy children (ages 1 – 5 years). See col. 6, lines 9 – 11. In contrast, strain NCIMB 41003 was isolated from washed sections of the gastrointestinal tract obtained during reconstructive surgery, as described in Example 1 of the subject application. Applicant's claimed strain was adherent to the healthy gastrointestinal tract of individuals with no associated pathology. Fecal flora (such as that represented by *Bifidobacterium longum* strain 6-1) represent the luminal contents of the distal large bowel (colon). In contrast, microflora adherent to the mucosa represent a highly specialized microenvironment. For example, strains adherent to the mucosa must be able to survive in a more aerobic environment than occurs in the

lumen. Further, adherent strains thrive in an immunologically hostile environment.

Bifidobacterium that are obtained from/represent different locations in the gastrointestinal tract (here, mucosa and lumen) are known to be different in their characteristics. As discussed above, the population of bifidobacteria in the gastrointestinal tract is known to be influenced by several factors, such as diet, antibiotics and stress. Further, “[g]eographic specificities in the composition of the bifidobacterial microflora have to be considered, too.” Reuter, Gerhard. *Current Issues in Intestinal Microbiology* 2001. 2(2): 50.

The Examiner states that “U.S 6,368,591 disclose (sic) the strain belonging to the genus of *Bifidobacterium* including strain *Bifidobacterium longum* strain 6-1 (CCTCC Number M 98004 (sic)) which produces immunomodulatory effects upon oral consumption or regulates immunologic function, decreases abnormal level of cytokine expression (col. 14, lines 43 - 60).....” (Office action, page 8). However, it is not possible to determine if this is, in fact, correct, since *Bifidobacterium longum* strain 6-1 is not assessed for its ability to produce immunomodulatory effects or ability to regulate immunologic function or decrease abnormal levels of cytokine expression. Rather, U.S 6,368,591 describes the results of administration of only a microbe *composition*, which includes at least three microorganisms: *Bifidobacterium longum* strain 6-1 (CCTCC Number M 98003); *Lactobacillus acidophilus* YIT 2004 (CCTCC Number M 98004) and *Streptococcus faecalis* YIT 0027 (CCTCC Number M 98005). There is no discussion of the effects of *Bifidobacterium longum* strain 6-1 administered alone. For example, at column 14, lines 43 – 60, which is cited by the Examiner in support of the statement that *Bifidobacterium longum* strain 6-1 “produces immunomodulatory effects upon oral consumption or regulates immunologic function, decreases abnormal level of cytokine expression (col. 14, lines 43 - 60).....,” U.S 6,368,591 actually describes “a method for regulating and enhancing immunologic function.... comprising administering to the subject an effective amount of the above microbe *compositions* and “a method for decreasing abnormally elevated cytokine IL-6 in a subject comprising administering to the subject an effective amount of the above microbe *compositions*.” (emphasis added) See also, col. 32, lines 22 – 26: “the microbe *composition* of this invention, by working together with lactulose, has the property of reducing the endotoxin and abnormally elevated cytokine IL-6 levels in cirrhosis patients.” (emphasis added) Here, too, the composition, of which *Bifidobacterium longum* strain 6-1 is a

component, was administered and its effects (not those of *Bifidobacterium longum* strain 6-1) assessed. The statement attributing to *Bifidobacterium longum* strain 6-1 the characteristics described above is not supported by the teachings of U.S. 6,368,591.

The Examiner also characterizes U.S. 6,368,591 as teaching "various pharmaceutical and food formulation comprising strain *Bifidobacterium* in amounts more than 10x6 cfu/g in viable and in non-viable form after some period of storage (table 2) together with additional health beneficial probiotic lactobacteria (col. 9, lines 33-36)." This reference does not seem to be correct. However, throughout U.S. 6,368,591, the discussion is of use of the microbe *composition* and not of *Bifidobacterium longum* strain 6-1 *alone*. The cited patent does not teach pharmaceutical and food formulations as characterized by the Examiner.

U.S. 6,368,591 does not anticipate Applicant's claimed invention as represented by claim 56 and claims dependent thereon, directly or indirectly. That is, it does not anticipate claims 56 - 62 and 72-88. Withdrawal of the rejection is respectfully requested.

Claims 56-62 and 72-88 are also rejected under 35 U.S.C. §103(a) as obvious over U.S. Patent No. 6,368,591. As discussed at length above, the cited patent does not describe the characteristics of *Bifidobacterium longum* strain 6-1, but, rather, describes the use and effects of a combination of microorganisms, one of which is *Bifidobacterium longum* strain 6-1. It is not possible to determine what the characteristics of *Bifidobacterium longum* strain 6-1 are, in view of the fact that it is not assessed or described on its own, but only in the context of the combination. Such combination cannot make the claimed invention obvious. Withdrawal of the rejection is respectfully requested.

Rejections under 35 USC §103(a)

Claims 56-88 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,077,504 and/or U.S. Patent No. 6,368,591 taken with WO 98/35014. The Examiner indicates that claims 56-62 and 72-88 are as explained above and claims 63-71 are further drawn to incorporation of *Lactobacillus salivarius* including the particular strain NCIMB 40829 (UCC 118) into formulations with *Bifidobacterium* strain NCIMB 41003 (UCC 35624). The cited U.S. patents are characterized as disclosing "the strains of *Bifidobacterium* having immunomodulatory effects and the formulations comprising the strains *Bifidobacterium* together

with additional probiotic cultures including lactobacteria having similar immunomodulatory effects. But they are lacking particular disclosure related to the use of *Lactobacillus* or *Lactobacillus salivarius* including particular strain UCC 118 as an additional probiotic lactobacteria in composition with the strains of *Bifidobacterium*.” The Examiner cites WO 98/35014 as teaching “*Lactobacillus* or *Lactobacillus salivarius* including particular strain UCC 118 and it teaches incorporation of this strain into the health promoting formulations/compositions” and concludes it would have been obvious “to substitute or to add the strain belonging to *Lactobacillus* or *Lactobacillus salivarius* including particular strain UCC 118 of the cited patent WO 98/35014 for/to the additional probiotic lactobacteria in the compositions with the strains belonging to *Bifidobacterium* taught by the cited documents US 6,077,504 and/or US 6,368,591 with a reasonable expectation of success” for the reasons set forth at pages 10 – 11 of the Office action.

It appears that this rejection under 35 U.S.C. 103(a) applies to claims 63 – 71, which are directed to formulations that comprise *Bifidobacterium* strain NCIMB 41003 in combination with *Lactobacillus* or *Lactobacillus salivarius* UCC 118. Claims 56-62 and 72-88 do not include such combination and, therefore, this rejection of these claims is not applicable to them. Applicant’s attorney respectfully requests clarification of the rejection as it is being applied to these claims. As discussed above, claim 56, on which all of the remaining claims being considered in this action depend, directly or indirectly, requires the *Bifidobacterium* strain deposited at the NCIMB under accession number 41003. U.S. 6,077,504 and/or U.S. Patent No. 6,368,591 do not teach or even suggest this strain and, further do not teach or suggest combination of a strain with the characteristics of NCIMB 41003 in combination with *Lactobacillus* or *Lactobacillus salivarius* UCC 118. As discussed at length above, U.S. 6,077,504 teaches two specific *Bifidobacterium* strains that are not Applicant’s claimed strain and, in fact, differ significantly from Applicant’s claimed strain in characteristics important to its activity in the claimed formulations. Further, U.S. 6,077,504 teaches compositions that “contain at least two or more lactic acid bacteria of a genus selected from the group consisting of *Streptococcus thermophilus* and *Bifidobacterium longum*.” (See, e.g., col. 4, lines 29 – 33). It teaches the combination of *Streptococcus thermophilus* and *Bifidobacterium longum* and does not teach or suggest NCIMB 41003 or the combination of *Bifidobacterium longum* in

combination with *Lactobacillus* or, particularly, *Lactobacillus salivarius* UCC 118. U.S. 6,368,591 teaches only a microbial composition that comprises at least three microbes; in that formulation, the *Bifidobacterium* strain is a specific strain deposited at the CCTCC and there is no additional suggestion or teaching of *Bifidobacterium* strains. Applicant disagrees that the "idea for combining them flows logically from their having been used individually in the prior art," as the Examiner asserts. If the cited prior art were combined with WO 98/35014, the resulting composition would comprise at least two or more lactic acid bacteria of a genus selected from the group consisting of *Streptococcus thermophilus* and *Bifidobacterium longum*, in the case of U.S. 6,077,5, or a microbial composition that comprises at least three microbes, one of which is a specific strain deposited at the CCTCC, in the case of U.S. 6,368,591. There is no teaching or suggestion in either cited patent of Applicant's strain NCIMB 41003 or of a formulation comprising a *Lactobacillus* strain in combination with the NCIMB 41003 strain.

Applicant respectfully requests that this rejection be withdrawn.

In view of the above amendments and arguments presented herein, Applicant believes the pending application is in condition for allowance and respectfully requests that the claims be allowed.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 23/2825, from which the undersigned is authorized to draw.

Respectfully submitted,



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